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Synthesis and Properties of 2,6-Diamino-8,2′-anhydro-8-mercapto-9-β-D-arabinofuranosylpurine

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2,6-Diamino-9-β-D-ribofuranosylpurine (I) was brominated with saturated bromine-water to the 8-bromo compound (II), which was tosylated at the 2′-hydroxygroup *via* the 2′,3′-O-dibutylstannylene compound (III). The resulting 2,6-diamino-8-bromo-9-(2′-O-tosyl-β-D-ribofuranosyl)-purine (IV) was cyclized with thiourea in *n*-propanol or 40% sodium hydrogen sulfide to give 2,6-diamino-8,2′-anhydro-8-mercapto-9-β-D-arabinofuranosylpurine (V) in yields of 40% and 80%, respectively. Alternatively, 8,2′-anhydro-8-mercapto-9-β-D-arabinofuranosylguanine (VI) was acetylated and chlorinated with phosphoryl chloride to give the 2-amino-6-chloropurine-8,2′-S-cyclonucleoside derivative (VIII), which was aminated with ammonia in methanol to afford the 2,6-diaminopurine cyclonucleoside (V) in a yield of 45%. Catalytic desulfurization of the cyclonucleoside (V) gave 2,6-diamino-9-(2′-deoxy-β-D-ribofuranosyl)-purine (IX). Some physical properties of these compounds were elucidated by ultraviolet (UV), nuclear magnetic resonance (NMR) and circular dichroism (CD) spectroscopy. The CD spectra of these nucleosides and cyclonucleoside were similar to those of the corresponding adenine nucleosides and cyclonucleoside in general.

Keywords——2,6-diaminopurine nucleosides; 2,6-diaminopurine-8,2′-S-cyclonucleoside; cyclization; UV; NMR; CD

2,6-Diaminopurine has been reported to possess inhibitory effects against viruses and bacteria.[1] Howard *et al.*[2,3] reported that synthetic poly(2-aminoadenylic acid) acted as an analog of poly(adenylic acid) and formed a double helix having the third hydrogen bond and a triple helix with poly (uridylic acid). Recently, Khudyakov *et al.*[4] found that 2,6-diaminopurine could completely substitute for adenine and formed a complementary base pair with thymine in cyanophage S-2L DNA.

In view of these findings, it seemed possible that 2,6-diaminopurine cyclonucleosides having a fixed conformation[5] due to anhydro linkage between the base and the sugar moiety might have biological activity. Thus, 2,6-diamino-8,2′-anhydro-8-mercapto-9-β-D-arabinofuranosyl purine (2,6-diaminopurine-8,2′-S-cyclonucleoside) (V) was synthesized and its physical properties were studied by ultraviolet (UV), circular dichroism (CD) and nuclear magnetic resonance (NMR) spectroscopy.

Ikehara *et al.*[6] recently reported a new method for synthesizing 8,2′-S-cyclonucleosides of adenine and guanine *via* 2′-O-tosyl-8-bromopurine nucleoside, which is obtainable from the 2′,3′-O-di-butylstannylene compounds of 8-bromoadenosine and guanosine. According to this method, 2,6-diaminopurine-8,2′-S-cyclonucleoside (V) was first prepared by cyclization of 2,6-diamino-8-bromo-9-(2′-O-tosyl-β-D-ribofuranosyl)-purine (IV) derived from 2,6-diamino-9-β-D-ribofuranosylpurine (I).

Several synthetic procedure for the compound (I) have been reported[7–10] but they involved rather lengthy pathways and seemed unsuitable for preparing the starting material of cyclonucleoside (V).

In this work, compound (I) was synthesized by amination of 2-amino-6-chloro-9-(2′,3′,5′-O-triacetyl-β-D-ribofuranosyl)-purine[11] with ammonia in ethanol at 100°C for 10 h in a yield of 54%. This material was identical with an authentic sample in mp, elemental analysis and paper chromatography in three solvent systems.

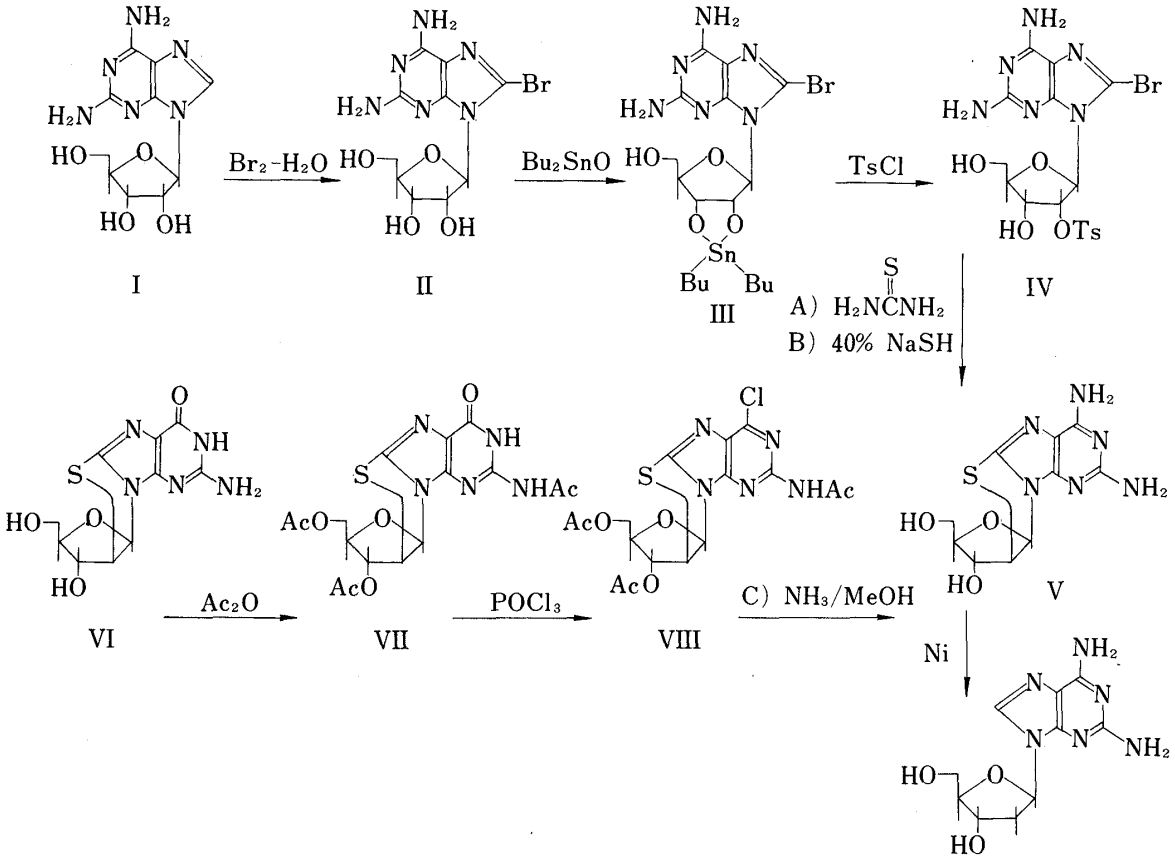

Chart 1

Next, compound (I) was brominated with saturated brominewater at room temperature for 1 h to give 2,6-diamino-8-bromo-9-β-D-ribofuranosylpurine (II) in a yield of 92%. UV absorption maxima at 262 and 283 nm MS fragment peaks of *m/e* 361 and 363 corresponding to the bromo derivative ion were seen. The NMR signal of H-8 at 7.92 ppm observed in compound(I), was no longer present, showing that the 8-carbon must be substituted by bromine.

Treatment of the bromo compound (II) with one equivalent of di-O-butyltin oxide in methanol for 5 h afforded 2,6-diamino-8-bromo-9-(2′,3′-O-dibutylstannylene-β-D-ribofuranosyl)-purine (III). Elemental analysis and UV absorption maxima at 262 and 285 nm supported the structure of the compound (III).

The 2,6-diamino-8-bromo-9-(2′-O-tosyl-β-D-ribofuranosyl)-purine (IV) was prepared in a yield of 56% by treatment of the crude dibutylstannylene compound (III) with seven equivalents of triethylamine and tosyl chloride. The NMR spectra signals at 2.28, 7.05 and 7.43 ppm assigned to a methyl group and protons of a tosyl group, respectively. A signal of H-2′ appeared at 5.73 ppm, showing that the 2′-carbon must be substituted.

The 8-bromo-2′-O-tosyl derivative (IV) was cyclized with thiourea in *n*-propanol at 150°C for 5 h or 40% sodium hydrogen sulfide in DMF at 60°C for 6 h to give 2,6-diaminopurine-8,2′-S-cyclonucleoside (V) in yields of 40% and 88%, respectively. The NMR spectra showed signals of H-1′ at 6.29 ppm and H-2′ at 4.77 ppm having a coupling constant $J_{1'-2'}=6.0$ Hz. which suggested the 8,2′-S-cyclonucleoside structure.[5] The mass spectra showed a molecular ion peak at *m/e* 296 together with a peak corresponding to 2,6-diamino-8-mercaptopurine at *m/e* 128, and UV absorption maxima were found at 264 and 292 nm.

For the synthesis of this cyclonucleoside (V), an alternate route was investigated. 8,2′-Anhydro-8-mercapto-9-β-D-arabinofuranosylguanine (8,2′-S-cycloguanosine) (VI)[6,12,13,14] was first acetylated as usual to give the N^2,3′,5′-O-triacetyl derivative (VII) in a yield of 88%.

The triacetyl compound (VII) was then chlorinated with phosphoryl chloride and N,N-diethylaniline. The reaction proceeded almost quantitatively and the chloro compound (VIII) was obtained in crude form; its UV absorption spectrum showed maxima at 225, 262 and 305 nm.

The crude chloro compound (VIII) was aminated by treatment with methanolic ammonia at 100°C for 15 h to give 2,6-diaminopurine-8,2′-S-cyclonucleoside (V) in a yield of 45%. The compound (V) proved to be identical with that obtained by the cyclization of 2,6-diamino-8-bromo-2′-O-tosylpurine riboside (IV) as described above.

The Raney-nickel desulfurization of the 2,6-diaminopurine-8,2′-S-cyclonucleoside (V) gave the corresponding 2,6-diamino-9-(2′-deoxy-β-D-riboufranosyl)-purine (IX)[10] in a yield of 18%. The UV absorption maxima at 256 and 280 nm and MS fragment ion of *m/e* 266 corresponding to the molecular ion of the 2′-deoxy derivative, confirmed the structure of the compound (IX).

The CD spectra of the synthesized 2,6-diaminopurine nucleosides and cyclonucleosides were measured in 0.01 M phosphate buffer solution at pH 7.0 and the results are summarized

TABLE I. CD Spectroscopic Data for 2,6-Diaminopurine Nucleosides and 8,2′-S-Cyclonucleosides

Compound	λ_{max}(nm)	$[\theta]$	λ_{min}(nm)	$[\theta]$
I	220	6.84[a]	250	−4.71
	270	−1.62	280	−1.69
II	220	6.50[a]	252	−4.59
	280	0.00	303	−0.57
V	240	−1.44[b]	258	−4.66
	282	0.79		
VI	230	−0.13[b]	255	−2.42
	290	1.06		
IX	265	−2.85[a]	250	−5.32
			279	−3.55

0.01 M phosphate buffer, pH 7.0.
a) $[\theta]\times10^{-4}$.
b) $[\theta]\times10^{-5}$.

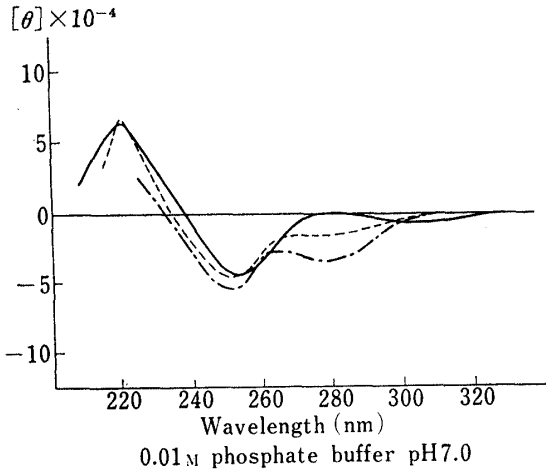

Fig. 1. CD Spectra of 2,6-Diaminopurine Nucleosides

———, 2,6-diamino-8-bromo-9-β-D-ribofuranosylpurine.
– – – – –, 2,6-diamino-9-β-D-ribofuranosylpurine.
—·—·—, 2,6-diamino-9-(2′-deoxy-β-D-ribofuranosyl)purine.

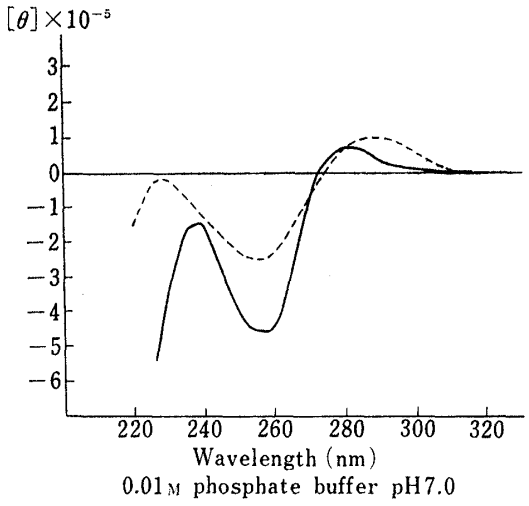

Fig. 2. CD Spectra of 8,2′-S-Cyclonucleosides

———, 2,6-diaminopurine-8,2′-S-cyclonucleoside.
– – – – –, 8,2′-S-cycloguanosine.

in Table I. The CD spectra of 2,6-diamino-8-bromopurine riboside (II), unsubstituted 2,6-diaminopurine nucleoside (I) and (IX), which have a ribofuranose or 2′-deoxyribofuranose sugar moiety, are compared in Fig. 1. 2,6-Diaminopurine riboside (I) and 2′-deoxyriboside (IX) gave a negative Cotton band at around the UV absorption maximum of 280 nm, whereas 2,6-diamino-8-bromopurine riboside (II) gave a positive one. These results are consistent with the general rules[15] concerning the CD profiles of the correpsonding adenine nucleosides. As shown in Fig. 2, the CD spectra of 2,6-diaminopurine-8,2′-S-cyclonucleoside (V) and 8,2′-S-cycloguanosine (VI) gave a positive Cotton band at arround 280—290 nm and a negative Cotton band at around 255—265 nm. As expected from previous observations on other purine-S-cyclonucleosides,[16–19] these compounds had a positive Cotton band in the B-region. These results are also consistent with purine cyclonucleoside structurs for compounds (V) and (VI).

Biological properties of these compounds are investigation and will be reported in a future publication.

Experimental

UV absorption spectra were taken with a Hitachi 340 spectrophotometer. IR spectra were taken with a JASCO IR-S spectrophotometer. NMR spectra were taken with a Hitachi R-22 spectrophotometer operated at 90 MHz. DMSO-d^6 was used as the solvent and tetramethylsilane was used as the internal reference. CD spectra were measured with a JASCO J-20 spectropolarimeter in a 10 mm pathlength cell using 0.01 M phosphate buffer solution (pH 7.0) with 1.5 OD of nucleoside. Mass spectra were taken with a JMS-D-100 spectrometer. TLC was performed on Kieselgel HF 254, developed with $CHCl_3$–EtOH mixture. Paper chromatography (PPC) was performed on Toyo Roshi filter paper No. 51-A in the following solvent systems: A, H_2O adjusted to pH 10 with NH_4OH; B, *n*-BuOH–H_2O (86: 14, v/v); C, iso-PrOH–conc. NH_4OH–H_2O (7: 1: 2, v/v).

2,6-Diamino-9-β-D-ribofuranosylpurine (I)——2-Amino-6-chloro-9-(2′,3′,5′-tri-O-acetyl-β-D-ribofuranosyl)purine[11] (2.5 g) was dissolved in absolute ethanol (100 ml) which had been saturated with ammonia gas for 30 min under cooling at −15°C. The mixture was sealed in a steel tube and heated at 100°C for 10 h. After removal of the solvent by evaporation *in vacuo*, the residue was recrystallized from water to give 590 mg (54%) of 2,6-diaminopurine riboside (I) as colorless prisms mp 240°C.[7–10] *Anal.* Calcd for $C_{10}H_{14}N_6O_4$: C, 42.55; H, 5.00; N, 29.78. Found: C, 42.36; H, 4.98; N, 29.73. UV $\lambda_{max}^{H_2O\ (pH\ 1)}$ nm (ε): 252 (11900), 290 (10400); $\lambda_{max}^{H_2O\ (pH\ 7.0)}$ 256 (9700), 280 (10400); $\lambda_{max}^{H_2O\ (pH\ 13)}$ 256 (9900), 280 (10500). NMR δ: 4.52 (1H, q, H-2′), 5.73 (1H, d, H-1′ $J_{1'-2'}=6.0$ Hz), 5.71 (2H, s, 2-NH_2), 6.75 (2H, s, 6-NH_2), 7.91 (1H, s, H-8). PPC: *Rf* (A) 0.33, *Rf* (B) 0.09, *Rf* (C) 0.31.

2,6-Diamino-8-bromo-9-β-D-ribofuranosylpurine (II)——Bromine (0.24 ml) was added to water (24 ml) and the mixture was stirred very vigorously until all the bromine had dissolved at room temperature. The saturated bromine-water was added dropwise to a solution of 2,6-diaminopurine riboside (I) (848 mg, 3 mmol) in water (5 ml). The reaction mixture was stirred at room temperature for 1 h. Then sodium bisulfite solution (5 M) was added with stirring until the colour of the reaction mixture changed from red to yellow. The pH of the solution was adjusted to 6—7 with 1 M sodium hydroxide. A pale yellow solid was precipitated at pH 4. The mixture was kept in a refrigerator overnight. Precipitated crystals were filtered off, successively washed with cold water (5 ml) and cold acetone (5 ml), and dried. The bromide (II) was obtained in a yield of 994 mg (92%). An analytical sample was recrystallized from water. mp>300°C. *Anal.* Calcd for $C_{10}H_{13}N_6O_4Br$: C, 33.25; H, 3.26; N, 23.27. Found: C, 33.17; H, 3.70; N, 23.55. UV $\lambda_{max}^{H_2O\ (pH\ 1)}$ nm (ε): 259 (14600), 294 (10700); $\lambda_{max}^{H_2O\ (pH\ 7.0)}$ 262 (11400), 283 (12600); $\lambda_{max}^{H_2O\ (pH\ 13)}$ 262 (11400), 283 (12600). MS *m/e*: 361, 363 (M^+). NMR δ: 3.61 (2H, m, H-5′), 4.93 (1H, m, H-4′), 4.44 (1H, m, H-3′), 5.36 (1H, d, 3′-OH), 5.60 (1H, d, 2′-OH), 5.02 (2H, m, H-2′ and 5′-OH), 5.70 (1H, d, H-1′, $J_{1'-2'}=6.0$ Hz), 5.71 (2H, s, 2-NH_2), 6.95 (2H, s, 6-NH_2). PPC: *Rf* (A) 0.22, *Rf* (B) 0.20, *Rf* (C) 0.47. TLC ($CHCl_3$: EtOH, 3: 1) *Rf* 0.40.

2,6-Diamino-8-bromo-9-(2′,3′-O-di-*n*-butylstannylene-β-D-ribofuranosyl)-purine (III)——2,6-Diamino-8-bromopurine riboside (II) (108 mg, 0.3 mmol) and di-*n*-butyltin oxide (75 mg, 0.3 mmol) were dissolved in methanol (7.5 ml) and the mixture was refluxed for 5 h, then cooled. The colorless precipitates were collected and recrystallized from acetone–ethanol mixture to give colorless crystals (44.2 mg, 25%). mp 221—223°C. *Anal.* Calcd for $C_{18}H_{29}N_6O_4SnBr \cdot 1/2H_2O$: C, 35.97; H, 5.03; N, 13.98. Found: C, 36.10; H, 5.14; N, 13.52. UV $\lambda_{max}^{50\%\ EtOH}$ nm: 218, 263, 285; $\lambda_{max}^{50\%\ EtOH(H^+)}$ 260, 290; $\lambda_{max}^{50\%\ EtOH(OH^-)}$ 263, 280. MS *m/e*: 229, 231 (2,6-diamino-8-bromopurine), 331—339 (dibutylstannyleneribose–CH_2OH).

2,6-Diamino-8-bromo-9-(2′-O-tosyl-β-D-ribofuranosyl)-purine (IV)——A mixture of 2,6-diamino-8-bromopurine riboside (II) (361 mg, 1 mmol) and dibutyltin oxide (250 mg, 1 mmol) in methanol (25 ml) was heated under reflux for 5 h. The mixture was cooled, then triethylamine (0.98 ml, 7 mmol) and tosyl chloride

(1.32 g, 7 mmol) were added successively, and the whole was stirred at room temperature for 1 h. The precipitate was removed by filtration and the filtrate was evaporated to dryness *in vacuo*. The residue was washed with water (30 ml) and ether–hexane (1: 1, 40 ml). Colorless crystals were obtained by recrystallization from methanol (288 mg, 56%). mp 213—216°C. *Anal.* Calcd for $C_{17}H_{19}N_6O_6SBr$: C, 39.62; H, 3.72; N, 16.31. Found: C, 39.83; H, 3.74; N, 16.55. UV $\lambda_{max}^{50\%\ EtOH}$ nm (ε): 221 (26300), 263 (10300), 285 (10500); $\lambda_{max}^{50\%\ EtOH(H^+)}$ 261 (13500), 295 (8700); $\lambda_{max}^{50\%\ EtOH(OH^-)}$ 263 (10500), 285 (10700). MS *m/e*: 514, 516 (M^+). NMR δ: 2.28 (3H, s, tosyl-CH_3), 5.75 (2H, s, 2-NH_2), 5.73, 5.78 (2H, m, H-1′, H-2′), 6.95 (2H, s, 6-NH_2), 7.05 (2H, d, Ts–Hb), 7.42 (2H, d, Ts–Ha). IR ν_{max}^{KBr} cm^{-1}: 1170 (covalent tosylate). TLC ($CHCl_3$: EtOH, 3: 1) *Rf* 0.82. PPC: *Rf* (A) 0.43, *Rf* (B) 0.77, *Rf* (C) 0.85.

N^2,3′,5′-O-Triacetyl-8,2′-S-cycloguanosine (VII)——8,2′-S-Cycloguanosine (VI)[6,12–14] (594.4 mg, 2 mmol) was dissolved in pyridine (12 ml). Acetic anhydride (5 ml) was added to the solution and the mixture was stirred for 48 h at room temperature. The extent of the reaction was examined by TLC ($CHCl_3$: EtOH, 9: 1) *Rf* 0.36. After removal of the solvent by evaporation *in vacuo*, the residue was co-evaporated with ethanol (15 ml × 3) to remove traces of acetic anhydride. The residue was recrystallized from ethanol to give the triacetyl compound (VII), mp>300°C, in a yield of 680 mg (88%). *Anal.* Calcd for $C_{16}H_{17}N_5O_7S \cdot 1/2H_2O$: C, 44.65; H, 4.18; N, 16.14. Found: C, 44.89; H, 4.10; N, 16.36. UV $\lambda_{max}^{50\%\ EtOH}$ nm: 270, 297 (sh), $\lambda_{max}^{50\%\ EtOH(H^+)}$ 270, 297 (sh), $\lambda_{max}^{50\%\ EtOH(OH^-)}$ 275. PPC: *Rf* (A) 0.84, *Rf* (B) 0.77, *Rf* (C) 0.85.

2-Acetamido-8,2′-anhydro-6-chloro-8-mercapto-9-(3′,5′-O-diacetyl-β-D-arabinofuranosyl)purine (VIII)——Well-dried N^2,3′,5′-O-triacetyl-8,2′-S-cycloguanosine (VII) (762.4 mg, 2 mmol) was added to a mixture of phosphoryl chloride (6 ml) and N,N-diethylaniline (0.3 ml). The mixture was refluxed for 5 min and phosphoryl chloride was distilled off *in vacuo*. To the residue, ice-water was added with stirring for 10—15 min. The mixture was extracted with dichloromethane (20 ml × 5) and the combined extracts were washed with cold water until the aqueous wash was neutral. The dichloromethane solution was dried over anhydrous sodium sulfate. Removal of the solvent by evaporation *in vacuo* gave a crude sample of 2-acetamido-8,2′-anhydro-6-chloro-8-mercapto-9-(3′,5′-O-diacetyl-β-D-arabinofuranosyl)purine (VIII) in almost quantitative yield. UV $\lambda_{max}^{50\%\ EtOH}$ nm: 225, 262, 305. $\lambda_{max}^{50\%\ EtOH(H^+)}$ 225, 262, 305, $\lambda_{max}^{50\%\ EtOH(OH^-)}$ 262, 309. TLC ($CHCl_3$: EtOH, 9: 1) *Rf* 0.52.

2,6-Diamino-8,2′-anhydro-8-mercapto-9-β-D-arabinofuranosylpurine (V)——a) A solution of 2,6-diamino-8-bromo-9-(2′-O-tosyl-β-D-ribofuranosyl)purine (IV) (156 mg, 0.36 mmol) and thiourea (84 mg, 1.1 mmol) in *n*-propanol (5.5 ml) was heated at 150°C for 5 h. The solution was evaporated to dryness *in vacuo* and the residue was applied to Whatman 3 MM paper and developed with water at pH 10. A band of *Rf* 0.21 was extracted with water and the extract was evaporated to dryness. The residue was recrystallized from water to give 2,6-diaminopurine-8,2′-S-cyclonucleoside (V) as colorless needles, mp 172—175°C, in a yield of 43 mg, (40%). *Anal.* Calcd for $C_{10}H_{12}N_6O_3S \cdot H_2O$: C, 38.22; H, 4.49; N, 26.74. Found: C, 38.49; H, 4.07; N, 26.79. UV $\lambda_{max}^{H_2O\ (pH\ 7.0)}$ nm (ε): 264 (12200), 292 (15900). $\lambda_{max}^{H_2O\ (pH\ 1)}$ 220 (17000), 264 (15900), 304 (13700), $\lambda_{max}^{H_2O\ (pH\ 13)}$ 264 (12300), 292 (16200). MS *m/e*: 296 (M^+), 248 ($M^+ - 48$), 128 (8-mercapto-2,6-diaminopurine). NMR δ: 3.91 (1H, m, H-4′), 4.34 (1H, m, H-3′), 4.77 (1H, q, H-2′, $J_{2'-3'}$=2 Hz), 5.80 (2H, s, 2-NH_2), 6.29 (1H, d, H-1′, $J_{1'-2'}$=6.0 Hz), 6.52 (2H, s, 6-NH_2). PPC: *Rf* (A) 0.21, *Rf* (B) 0.18, *Rf* (C) 0.71. TLC ($CHCl_3$: EtOH, 3: 1) *Rf* 0.24.

b) The 2′-O-tosyl compound (IV) (130 mg, 0.25 mmol) was dissolved in anhydrous DMF (2.5 ml) and N_2 gas was bubbled through the solution for 15 min. Then 40% sodium hydrogen sulfide aqueous solution was added and the mixture was heated at 60°C for 6 h. The reaction mixture was neutralized with 1 N HCl and the solvent was evaporated off *in vacuo*. The residue was applied to Whatman 3MM paper in water (pH 10) and worked up as above. The cyclonucleoside (V) was obtained in a yield of 65 mg, (88%). This sample was identical with that obtained in a).

c) The crude 2-acetamido-8,2′-anhydro-6-chloro-8-mercapto-9-(3′,5′-O-diacetyl-β-D-arabinofuranosyl)-purine (VIII) (956 mg, 2.1 mmol) was dissolved in methanol (60 ml) and ammonia gas was bubbled through the solution for 30 min, under cooling at −15°C. The mixture was sealed in a steel tube and heated at 100°C for 15 h. After removal of the solvent by evaporation *in vacuo*, the residue was applied to Whatman 3MM paper and worked up as above. The cyclonucleoside (V) was obtained in a yield of 290 mg, (45%). This sample was identical with the samples obtained in a) and b).

2,6-Diamino-9-(2′-deoxy-β-D-ribofuranosyl)purine (IX)——2,6-Diamino-8,2′-anhydro-8-mercapto-β-D-arabinofuranosylpurine (V) (100 mg, 0.34 mmol) was dissolved in water (10 ml). Raney nickel[20] (1 ml) was added to the solution and the mixture was refluxed for 3 h with vigorous stirring. The Raney nickel was filtered off and washed with boiling water. The filtrate and washings were combined and evaporated to dryness *in vacuo*. The residue was applied to Whatman 3MM paper and developed with water at pH 10. A band at *Rf* 0.31 was extracted with water to give 16 mg (18%) of colorless needles, mp 140—145°C (lit.[10] 146—148°C) and gave a pink color with cysteine-sulfuric acid spray on the paper chromatogram. UV $\lambda_{max}^{H_2O\ (pH\ 1)}$ nm: 258, 290. $\lambda_{max}^{H_2O\ (pH\ 7.0)}$ 256, 280. $\lambda_{max}^{H_2O\ (pH\ 13)}$ 256, 280. MS *m/e*: 266 (M^+). PCC: *Rf* (A) 0.31, *Rf* (B) 0.18, *Rf* (C) 0.71.

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